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REC'D 18 MAR 1999

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Request for grant of a Patent Form 1/77

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① Title of invention

Pharmaceutical Formulation

- 1 Please give the title of the invention

② Applicant's details☐ **First or only applicant**

- 2a If you are applying as a corporate body please give:

Corporate name

Pharma Mar, S. A.

Country (and State of incorporation, if appropriate)

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- 2c In all cases, please give the following details:

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Country

ADP number (if known)

43811 410012

PHARMACEUTICAL FORMULATION

The present invention relates to a pharmaceutical formulation, and more particularly a pharmaceutical formulation of a didemninn.

THE BACKGROUND

US Patent 5,294,603 to Rinehart claims a pharmaceutical composition comprising a didemninn, in combination with a pharmaceutically acceptable carrier, excipient or diluent. In that patent, extensive results are given for testing for biological activity, notably assay results for cytotoxicity and antiviral activity. No examples are provided of the claimed pharmaceutical composition and no information is given regarding the identity of the pharmaceutically acceptable carrier, excipient or diluent.

THE PROBLEM

In practice, there are some difficulties in preparing pharmaceutical compositions of didemnins suited for administration to patients, and especially a need for a stable parental pharmaceutical dosage form.

THE INVENTION

The present invention provides a pharmaceutical composition of a didemninn, comprising firstly a lyophilised didemninn preparation and secondly a reconstitution solution.

surfactant is suitably 10 to 25 % v/v of the mix; the alkanol is suitably 10 to 25 % v/v of the mix; and the water is suitably 50 to 80 % v/v of the mix.

EXAMPLES

Freeze-drying was performed from a 1.0 mg/ml solution aplidine in 40% v/v t-butanol in water for injection ("WFI") containing 25 mg/ml mannitol as bulking agent. Differential scanning calorimetry studies were conducted to determine the freeze-drying cycle parameters. The prototype, containing 1.0 mg aplidine and 25 mg mannitol per vial was found to be the optimal formulation in terms of solubility, length of the freeze-drying cycle and dosage requirements.

A solution composed of 15/15/70% (v/v/v) Cremophor EL/ethanol absolute/WFI was found to be the optimal reconstitution solution, Cremophor EL being a glycerol-polyethylene glycol ricinoleate available from BASF in Germany.

Dilutions of reconstituted product with normal saline up to 1:200 showed it to be stable for at least 24 hours after preparation. Quality control of the freeze-dried formulation demonstrated that the manufacturing process does not change the integrity of aplidine. Shelf-life data, available thus far, show that the formulation is stable for at least 6 months when stored at +4°C in the dark.

Thus, the preferred aplidine product of this invention is a dual-package containing:

- an injection vial containing aplidine 1 mg/vial lyophilized product, and
- an injection vial containing 2 ml of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstitution solution.

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